

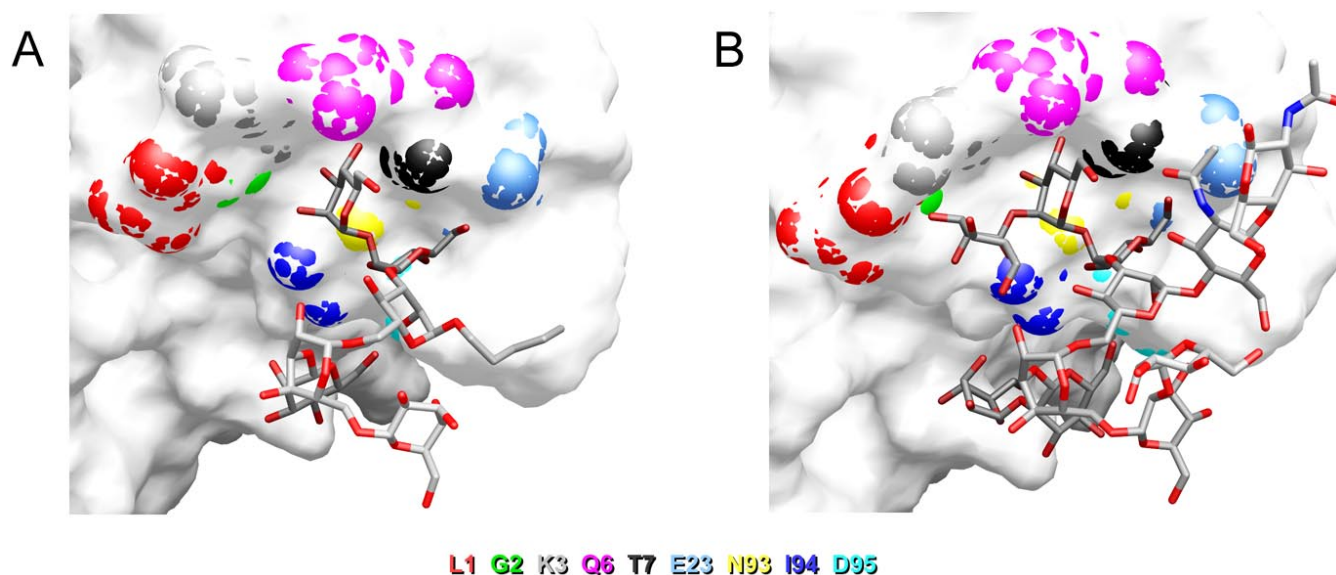
Abstract No. Boto0044

Structures of the Complexes of a Potent Anti-HIV Protein Cyanovirin-N and High-Mannose Oligosaccharides

I. Botos (NCI), B. O'Keefe (NCI), S. Shenoy (NCI), L. Cartner (SAIC), D. Ratner (MIT), P. Seeberger (MIT), M. Boyd (U. South Alabama, Mobile), and Alexander Wlodawer (NCI)
Beamline(s): X9B

Introduction: The development of anti-HIV microbicides for either topical or *ex vivo* use is of considerable interest, mainly due to the difficulties in creating a vaccine that would be active against multiple clades of HIV. Cyanovirin-N (CV-N), an 11kDa protein from the cyanobacterium (blue-green algae) *Nostoc ellipsosporum* with potent virucidal activity was identified in the search for such antiviral agents. The binding of CV-N to the heavily glycosylated HIV envelope protein gp120 is carbohydrate-dependent. Since previous CV-N – dimannose structures could not fully explain CV-N/oligomannose binding, we determined the crystal structures of recombinant CV-N complexed to Man-9 and a synthetic hexamannoside, at 2.5 Å and 2.4 Å resolution, respectively. CV-N is a three-dimensionally domain-swapped dimer in the crystal structures, with two primary sites near the hinge region, and two secondary sites on the opposite ends of the dimer. The binding interface is constituted of three stacked $\alpha 1 \rightarrow 2$ linked mannose rings for Man-9 and two stacked mannose rings for hexamannoside, with the rest of the saccharide molecules pointing to the solution. These structures show unequivocally the binding geometry of high-mannose sugars to CV-N, permitting a better understanding of carbohydrate binding to this potential new lead for the design of drugs against AIDS.

Acknowledgments: We would like to thank L.Barrientos and A.Gronenborn for helpful discussions. P.S. is a Glaxo-Smith-Kline Research Scholar and an Alfred P. Sloan Scholar. D.R. is supported financially by the NIH Biotechnology Training Grant.



Structure of oligosaccharides bound to cyanovirin-N. (A) The complex with hexamannoside, with a binding interface of two stacked mannose rings; (B) The complex with Man-9, with an interface consisting of three stacked mannose rings. The protein residues in contact with carbohydrates are color coded.